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Long-Term Exposure to Air Pollution and Incidence of Type 2 Diabetes in the Nurses' Health Study and Nurses' Health Study II

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Background: Research has detected associations between air pollution exposure and type 2 diabetes (T2DM), but findings from large cohort studies are needed to ascertain the most influential pollutants, susceptible subpopulations, and low-level exposure associations. Our aim was to prospectively evaluate the association between long-term exposure to fine particulate matter <2.5 μm in aerodynamic diameter ($PM_{2.5}$) and nitrogen dioxide (NO_2) and T2DM incidence in the Nurses' Health Study (NHS) and Nurses' Health Study II (NHSII) cohorts of US women.

Methods: Monthly $PM_{2.5}$ and NO_2 exposures were predicted from spatiotemporal models and linked to participants' residential addresses. We used Cox proportional hazards models to assess the association between 24-month moving average $PM_{2.5}$ and NO_2 exposure and self-reported, clinician-diagnosed T2DM from 1992–2019. We adjusted for time-varying lifestyle factors, reproductive hormonal factors, and individual and neighborhood socioeconomic status (SES). Results were meta-analyzed. We evaluated whether relationships persisted at levels below the current US EPA National Ambient Air Quality Standards (NAAQS). Lastly, we examined multiplicative and additive interactions by body mass index (BMI), smoking status, physical activity, neighborhood SES, and region.

Results: Over follow-up, there were 19,083 incident T2DM cases among the 208,733 women in NHS and NHSII. In fully adjusted single-pollutant models, the hazard ratio (HR) for an interquartile range (IQR) (IQR = 4.9 $\mu g/m^3$) higher 24-month average $PM_{2.5}$ exposure was 1.05 [95% confidence interval (CI): 1.02, 1.08] for incident T2DM. The HR for an IQR (7.3 ppb) higher NO_2 exposure was 1.05 (95% CI: 1.01, 1.09). Both associations were robust to co-adjustment. Associations remained stable when restricting to $PM_{2.5}$ levels below the NAAQS as compared to the full dataset. Stronger associations were observed in individuals who had a BMI ≥30, were physically active, and resided in the Northeast.

Conclusions: Our results showed a positive association between T2DM and long-term exposure to $PM_{2.5}$ and NO_2, persisting even at levels below the current EPA NAAQS. https://doi.org/10.1289/EHP15673

Introduction

The United Nations has recognized type 2 diabetes mellitus (T2DM) as a major public health threat.[1] Global prevalence of T2DM has continuously increased over the past four decades, affecting an estimated 8% of adults.[2] The International Diabetes Federation estimates that more than $1 trillion was spent on diabetes and its cardiovascular complications in 2025 alone.[3] Exposure to air pollution has been associated with a variety of adverse health outcomes, including respiratory disease, cardiovascular disease, and cancer, and has been estimated to be responsible for millions of deaths per year worldwide.[4–8] Epidemiologic evidence on the associations between long-term air pollution exposures and incident T2DM is growing.[9–17] Toxicological studies have identified potential biological mechanisms involving inflammation, impaired glucose metabolism, oxidative stress, and insulin resistance.[18] However, more large, prospective cohort studies are needed to identify the most influential pollutants as well as to assess associations at low levels of air pollution exposure and in susceptible populations. While earlier air pollution–T2DM research has assessed effect measure modification (EMM) on the multiplicative scale, the additive scale is better suited for identifying targets of public health intervention and for understanding biological mechanisms.[19,20]

Our previous study among northeastern and midwestern participants in the US-based Nurses' Health Study (NHS) and Health Professionals Follow-up Study (HPFS) cohorts was one of the first prospective cohort studies to examine the association between long-term air pollution exposure and T2DM.[21] Among women, we did not find strong evidence of an association between incident T2DM and particulate matter (PM), but we observed a positive association with distance to road, a proxy for traffic-related exposure. Subsequently, other investigators have examined the association of T2DM with PM and other pollutants including nitrogen dioxide (NO_2), sulfur dioxide, ozone, and other proxies for traffic-related exposures. Meta-analyses have shown

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the strongest associations of T2DM with exposure to PM <2.5 μm in aerodynamic diameter ($PM_{2.5}$), PM <10 μm in aerodynamic diameter (PM_{10}), and NO_2 with T2DM prevalence; in contrast, only $PM_{2.5}$ was associated with T2DM incidence.[22,23] However, past studies have varied in their design and measurement techniques and have not consistently implicated the same pollutants.[22–25] Reviews on this topic emphasize the need for prospective cohort studies with robust confounding control and exposure measurement, joint adjustment for co-pollutants, and ability to identify potentially vulnerable and susceptible populations.[18,22]

To address these research gaps, we prospectively evaluated the association between long-term air pollution exposure and T2DM incidence in two cohorts of women—NHS and Nurses' Health Study II (NHSII)—over 27 years of follow-up. Advancing from our 2011 regional study, in this nationwide analysis leveraging multiple-exposure models and adjustment for additional confounders, we focused on long-term exposures to $PM_{2.5}$ and NO_2. We selected these pollutants as they have the most consistent evidence in the literature, and NO_2 serves as a proxy for traffic-related exposure, building on the findings of our 2011 study.[21] We also evaluated EMM by individual- and area-level factors on the multiplicative and additive scales and examined various exposure time windows. Finally, we assessed the linearity of pollutant-T2DM relationships, and investigated relationships between $PM_{2.5}$, NO_2, and T2DM at levels below the current US Environmental Protection Agency (EPA) annual National Ambient Air Quality Standards (NAAQS) to assess if these new standards are sufficiently protective for T2DM.

Methods

Study Population

NHS and NHSII are prospective cohort studies of US women. NHS enrolled 121,700 female registered nurses 30–55 years of age in 1976, and NHSII enrolled 116,686 female registered nurses 25–42 years of age in 1989. While NHS participants were initially recruited from 11 states (California, Connecticut, Florida, Maryland, Massachusetts, Michigan, New Jersey, New York, Ohio, Pennsylvania, and Texas) and NHSII from 14 states (California, Connecticut, Indiana, Iowa, Kentucky, Massachusetts, Michigan, Missouri, New York, North Carolina, Ohio, Pennsylvania, South Carolina, and Texas), participants in both studies now reside throughout the conterminous US. Participants returned biennial questionnaires with rich covariate and health outcome data. A response rate of ≥90% for NHS and 85–90% for NHSII has been recorded for most follow-up cycles.[26]

For the current analyses, follow-up began in 1992 and ended in 2019 based on availability of confirmed case data. Participants who reported any nongestational diabetes ($n = 7,584$), including both T2DM and Type 1 diabetes, or cancer diagnoses except nonmelanoma skin cancer ($n = 14,781$) prior to the start of this analysis were excluded from the study population. The study was approved by the institutional review board of Brigham and Women's Hospital, and informed consent was implied through completion and return of the questionnaires.

Ascertainment of T2DM

On each questionnaire, participants reported whether they had received a physician diagnosis of T2DM. On first report of a new diagnosis, cases were confirmed through a validated supplementary questionnaire where participants answered questions on diabetes symptoms, diagnostic tests, and treatment. Before 1998, to be considered a confirmed diabetes case, participants had to meet the National Diabetes Group criteria, as follows: *a*) elevated plasma glucose concentrations on at least two different occasions, *b*) one or more diabetes symptoms (e.g., weight loss, thirst, polyuria, hunger) and a single elevated plasma glucose concentration, or *c*) treatment with hypoglycemic medication. After 1998, the American Diabetes Association (ADA) criteria were applied to identify cases, lowering the threshold for fasting glucose from 7.8 mmol/L to 7.0 mmol/L.[27] Since 2010, a hemoglobin A1c (HbA1c) ≥6.5% has been added to the ADA diagnosis criteria. Cases were considered questionnaire-confirmed T2DM if they met the stated diagnosis criteria. Consistent with other diabetes studies in the NHS and NHSII cohorts, only questionnaire-confirmed T2DM cases were included in this study.[28]

Exposure Assessment

Address histories were updated in each cohort during each biennial questionnaire cycle. All addresses have been geocoded, and exposures were predicted at the address level. Our primary metric of exposure was time-varying 24-month moving average exposures at location of residence from analytic study time start (1992) forward. In supplemental analyses, we explored alternative time windows, including cumulative average exposure over the follow-up period and exposure in the baseline year only.

Particulate matter. $PM_{2.5}$ predictions were estimated from generalized additive mixed models previously developed to estimate spatial and temporal gradients (and associated uncertainties) in monthly $PM_{2.5}$ levels for any point location in the conterminous US from January 1988 through December 2017. Previous publications have detailed the methods for $PM_{2.5}$ model development and validation.[29,30] Briefly, the models use nationwide monitoring data and information on nearby point sources, urban land use, elevation, and time-varying meteorological variables. To represent local traffic-related $PM_{2.5}$, models used distance to road terms prior to 2011 and traffic-related PM model output from a line-source dispersion model, ADMS-Roads, after 2011.[30] In terms of monitoring inputs, EPA monitoring data were not available for $PM_{2.5}$ prior to 1999. Therefore, $PM_{2.5}$ levels for 1988–1998 were predicted using pre-1999 PM_{10} levels, post-1999 $PM_{2.5}$: PM_{10} ratios, and airport visibility data.[31] Overall, cross-validation revealed the monthly average $PM_{2.5}$ models had high predictive accuracy (R^2 value of 0.77) and minimal bias across all years.[29]

Nitrogen dioxide. NO_2 predictions were estimated at precise participant residential locations using regionalized weekly spatiotemporal models for the contiguous US from 1990 onward based on an extension of universal kriging incorporating local temporal trends and smoothing via spatially correlated but temporally independent kriging of residuals, averaged to the month for this analysis.[32,33] The models drew on monitoring data from the EPA's Air Quality System, investigator deployed monitoring at more than 900 sites across the country plus tropospheric NO_2 satellite data from the Ozone Monitoring Instrument on the Aurora satellite. Partial least square regression was used to select features of geographic covariates from a set of 800 variables in order to explain variability in measured concentration, and these covariates were calculated at each participant's home address to create individual exposure predictions. Cross-validation of the NO_2 models revealed high predictive accuracy (R^2 value of 0.87).[33]

Covariates

Potential confounders were selected *a priori* from risk factors for T2DM or predictors of exposure.[21,34,35] On NHS/NHSII baseline questionnaires, we collected participants' family history of diabetes (yes/no) as well as their race (white, black, American Indian, Asian, Hawaiian, other/unknown, or multiracial) and

ethnicity (Hispanic or non-Hispanic) as a proxy for the experience of structural racism and discrimination. As our study population was mostly (93%) non-Hispanic white, due to small sample size, we collapsed the black, American Indian, Asian, Hawaiian, other/unknown, and multiracial responses into one category for purposes of analysis (white yes/no), though we acknowledge that doing so masks the diversity within these groups. The following time-varying covariates were updated using data from biennial questionnaires: smoking status (never, former, or current), smoking pack-years (continuous), and use of postmenopausal hormones (PMH) (never, former, or current). Census region of residence (Northeast, Midwest, South, or West) was determined for each residential address. We used self-reported height and weight to calculate body mass index (BMI) (<25.0, 25.0–29.9, or $\geq$30.0 kg/m^2).[36] As time-varying BMI might be a mediator on the pathway from air pollution to T2DM, we used analytic study time baseline (1992) BMI as a covariate in the main models. In EMM analyses, we employed time-varying BMI instead.

Physical activity and diet were updated on a 4-year schedule. Time spent per week in a variety of recreational activities was assessed and converted into measures of metabolic equivalent (MET) hours per week.[37] We created quartiles of cumulative average METs specific to each questionnaire cycle. A validated Food Frequency Questionnaire (FFQ) was used to calculate cumulative average alcohol consumption (0, 0.1–14.9, 15.0–29.9, or $\geq$30 g/day) and the Alternative Healthy Eating Index (AHEI) score (a measure of overall diet quality; range: 0 to 110, where 110 indicates maximum adherence).[38]

We also accounted for individual and neighborhood socioeconomic status (SES). At the individual level, we included marital status (married or divorced/separated/widowed/never married), spouse's educational attainment (more than high school, less than high school, or missing), and father's occupation (professional/manager or not professional/manager). At the neighborhood level, a composite score was created using selected variables from the US Census (1990, 2000, or 2010) closest to the time of each address.[39] The nine census tract level variables considered for inclusion represented domains that have previously been associated with health outcomes, namely, education, employment, housing, poverty/wealth, racial composition, and population composition. Each variable was z-standardized and summed to create a neighborhood SES (nSES) score, where increasing score is representative of increasing SES. The nSES range was −29 to 51.84 in NHS and −31.7 to 45.88 in NHSII. Information on population density was also obtained at the census tract level for the closest US Census (1990, 2000, or 2010) for each residential address over time.

We addressed missingness in covariates by carrying forward the value from the previous cycle. If still missing, the covariate was set to the reference level for categorical variables, to the median level for AHEI score and nSES, and to zero for smoking pack-years.

Statistical Analysis

In descriptive analyses, we examined covariates during follow-up from 1992 to 2019, overall and by levels of $PM_{2.5}$ and NO_2 exposure. Pearson correlations between pollutants and across time periods (24-month moving average, cumulative from the start of follow-up in 1992, and at analytic study time baseline in 1992) were also considered. Cohort-specific time-varying Cox proportional hazards models were used to evaluate the associations between $PM_{2.5}$ and NO_2 exposures and incident T2DM. To address nonproportionality, all models were stratified by age and calendar year to allow for different baseline hazards. Consistent with other literature on this topic, a 24-month moving average exposure window was selected to capture long-term exposure effects, as there is no definitive time window of biological relevance.[18] Person-time of follow-up was calculated in months from June 1992 in NHS and June 1993 in NHSII through whichever happened earliest: *a*) first diagnosis of diabetes or *b*) censoring by loss to follow-up, death, or the end of follow-up in December 2019. If any exposure data were missing, participants were excluded from the analysis only during those periods.

For each exposure, we estimated basic hazard ratios (HRs) and 95% confidence intervals (CIs) for an average interquartile range (IQR) difference in exposure ($PM_{2.5}$ IQR: 4.9 $\mu g/m^3$; NO_2 IQR: 7.3 ppb) adjusted for census region. IQRs were calculated across the entire study period from 1992 to the end of follow-up. Fully adjusted models included all *a priori* selected potential confounders. Basic models were stratified by age and calendar year and adjusted for census region. HRs and 95% CIs derived from cohort-specific models (i.e., NHS and NHSII) were pooled using random-effects meta-analysis. Cochran's Q was used for determining heterogeneity.[40] In addition to single exposure models, we applied two-pollutant basic and fully adjusted models to assess whether associations were robust to co-exposures.

To investigate the influence of individual covariates or groups of covariates on the effect estimation, and to inform model building, we ran additional models on the basis of the basic model with further adjustment for: *a*) individual factors [race, family history of diabetes mellitus (DM), smoking status, pack-years, BMI, physical activity, diet, alcohol use, and PMH use], *b*) individual SES (marital status, spouse's education level, father's occupation status), or *c*) neighborhood SES, each set of variables at a time. We repeated evaluation of the influence of the same covariates or groups of covariates in the two-pollutant models. To assess associations between pollutant exposures and T2DM incidence at low levels of exposure, we restricted the dataset to the observations (i.e., 24-month exposure windows) for each participant where $PM_{2.5}$ and NO_2 concentrations were below the current annual EPA NAAQS (9 $\mu g/m^3$ for $PM_{2.5}$ and 53 ppb for NO_2).[41]

EMM on the multiplicative scale was assessed by adding multiplicative interaction terms to the single exposure, multivariable models for each cohort, assessing statistical significance ($\alpha = 0.05$) and obtaining stratum-specific estimates by time-varying BMI status (<30 kg/m^2 or $\geq$30 kg/m^2), smoking status (never or current/former smoker), physical activity (below or above the median), nSES (below or above the median), and census region. EMM on the additive scale was evaluated by estimating relative excess risk due to interaction (RERI) for the same potential modifiers and testing for statistical significance ($\alpha = 0.05$).[42] For RERI analysis, the reference levels for the stratification variables were defined as BMI <30, never smoker, physical activity below the median, and nSES below the median, respectively. RERI for each region was assessed relative to the other regions.

We tested for deviations from linearity using restricted cubic splines.[43] Tests for nonlinearity used the likelihood ratio test, comparing the model with only the linear term to the model with the linear and cubic spline basis terms. In sensitivity analyses to assess the robustness of our models to differences in exposure conceptualizations, we considered models with cumulative average pollutant exposures since baseline (1992 onwards), baseline year exposure only (1992), and models restricted to participants who did not change addresses during follow-up from 1992 through 2019 ($n = 170{,}588$). To place our findings in the context of the existing literature on air pollution and T2DM incidence, we rescaled the fully adjusted single-pollutant model results per

10 $\mu g/m^3$. Statistical analyses were performed using SAS (version 9.4; SAS Institute Inc.).

Results

Our analyses included 97,029 participants from NHS and 111,704 from NHSII. Characteristics of the participants overall and for the top and bottom quintiles of $PM_{2.5}$ and NO_2 throughout follow-up are presented in Table 1. The majority of participants in both cohorts were non-Hispanic white, had no family history of T2DM, and lived in the Northeast or Midwest. The 24-month average $PM_{2.5}$ was similar across cohorts: 12.1 $\mu g/m^3$ [standard deviation (SD): 3.4] in NHS and 11.8 $\mu g/m^3$ (SD: 3.4) in NHSII. The same was true for NO_2 exposures, with 24-month averages of 10.6 ppb (SD: 6.6) in NHS and 10.5 ppb (SD: 6.5) in NHSII. The Pearson correlation between 24-month average $PM_{2.5}$ and NO_2 was moderate ($r = 0.50$ in NHS and $r = 0.58$ in NHSII) (Table S1). In both cohorts, those in the highest quintile of $PM_{2.5}$ or NO_2 exposure were younger, less physically active, less likely to have moved during follow-up, and slightly less likely to identify as non-Hispanic white (Table 1). Participants with higher exposures were also less likely to be married, resided in more densely populated areas, and areas with higher neighborhood SES.

We observed 19,083 cases of incident T2DM during follow-up (9,702 in NHS and 9,381 in NHSII). The concentration–response curves showed a monotonically increasing linear shape within the densely distributed ranges of the exposures, extending down to the lowest exposure levels (Figures S1 and S2). We therefore present linear exposure effect estimates. In single-pollutant basic models adjusted only for age, calendar year, and region, we observed a higher risk of T2DM incidence with higher 24-month moving average $PM_{2.5}$ and NO_2 exposure in both cohorts (Table 2). In fully adjusted single-pollutant analyses, associations with $PM_{2.5}$ were somewhat attenuated, while associations with NO_2 remained the same. The fully adjusted meta-analyzed HR for an IQR (4.9 $\mu g/m^3$) difference in 24-month average $PM_{2.5}$ exposure was 1.05 (95% CI: 1.02, 1.08). The meta-analyzed HR for an IQR (7.3 ppb) difference in NO_2 was similar (1.05; 95% CI: 1.01, 1.09). Figure 1 shows the impact of adjustment for each group of covariates on the observed associations. The HR for $PM_{2.5}$ was attenuated by individual factors, particularly baseline BMI and time-varying alcohol use. The HRs for $PM_{2.5}$ and NO_2 were both greater after adjusting for neighborhood SES.

In two-pollutant models (Table 2), both HRs for $PM_{2.5}$ and for NO_2 attenuated slightly [1.03 (95% CI: 1.00, 1.06) for $PM_{2.5}$ and 1.03 (95% CI: 1.00, 1.07) for NO_2]. Analogous to the model building Figure 1 shown for single-pollutant models, the individual influence of covariates on the two-pollutant model basic HRs is shown in the supplemental materials (Figure S3). Stepwise adjustment for nSES over the basic two-pollutant model increased the NO_2 HR, whereas the $PM_{2.5}$ HR was again most attenuated by adjustment for BMI and alcohol use.

When we restricted the dataset to exposures below the current EPA $PM_{2.5}$ NAAQS, the dataset was substantially smaller relative to the full exposure dataset ($n = 118{,}480$ vs. 208,733; person-years = 938,342 vs. 4,373,398) (Table S2). In contrast, the dataset restricted to exposures below the NO_2 NAAQS was only slightly smaller than the overall dataset. For both low-level exposure datasets, there was still evidence of positive T2DM associations for both exposures (Table 2). Associations with an IQR (1.6 $\mu g/m^3$) increase in $PM_{2.5}$ remained robust though with wider CIs in analyses restricted to the lower levels, with a meta-analyzed HR of 1.05 (95% CI: 0.95, 1.16) in single-pollutant models compared to 1.05 (95% CI: 1.02, 1.08) for the full range of exposure (IQR = 4.9 $\mu g/m^3$). Most exposures to NO_2 were below the current NAAQS; therefore, results from the threshold-restricted and full dataset models were very similar.

There was evidence of EMM on the multiplicative scale by time-varying BMI in the association between $PM_{2.5}$ and T2DM at the 0.05 alpha level, with p-for-interaction <0.01 in both cohorts (Table 3). In models stratified by time-varying BMI status, stratum-specific estimates were stronger among individuals with a BMI $\geq 30\ kg/m^2$ as compared to individuals with a BMI $<30\ kg/m^2$. There was no evidence of EMM by smoking status in the association between T2DM and either exposure or by physical activity in the association between T2DM and NO_2. For $PM_{2.5}$ and T2DM, estimates remained elevated only among individuals with physical activity levels above the median (Q3 and Q4). As for EMM by area-level factors, the multiplicative interaction terms for neighborhood SES and region were not statistically significant, except for region in the association between $PM_{2.5}$ and T2DM in NHS. A higher HR was consistently observed among individuals residing in the Northeast compared to other regions.

Our evaluation of EMM on the additive scale revealed evidence of an interaction by time-varying BMI (p-for-interaction <0.01) in the association between $PM_{2.5}$ and T2DM in both cohorts as well as in the association between NO_2 and T2DM in both cohorts (Table 4). In both cases, positive RERI was observed for participants with higher BMI, suggesting super-additive interactions, i.e., a positive departure from additivity of the associations of each pollutant and BMI with T2DM. There was evidence of an additive interaction by physical activity (p-for-interaction <0.01), with positive RERI for individuals with greater physical activity levels. The additive interaction term was statistically significant for nSES in the association between $PM_{2.5}$ and T2DM in NHSII (with positive RERI for individuals living in neighborhoods with nSES below the median—Q1 and Q2). We also found greater risk for the Northeast region relative to the other regions in the association between $PM_{2.5}$ and T2DM in NHS and between NO_2 and T2DM in NHSII.

In sensitivity analyses, models using cumulative average exposure since baseline or baseline year exposure only instead of the 24-month moving average, or restricting to nonmovers, exhibited findings similar to the main results (Tables S3–S5). Relative to 24-month moving average exposures for the same pollutant, cumulative average exposures were strongly correlated ($r > 0.85$), and baseline year exposures were moderately correlated ($r > 0.5$) (Table S1). As for the exposure distribution across time windows, baseline year levels for both pollutants were the highest, followed by cumulative average exposures (Table S6). Table S7 provides the numeric data used to generate Figure 1 and Figure S3.

Discussion

In these US-based prospective cohort studies of 208,733 women followed for 27 years, single-pollutant models suggested that an IQR increase in 24-month moving average $PM_{2.5}$ or NO_2 exposure was associated with a 5% increase in risk of incident T2DM, even after adjusting for a rich set of individual and area-level covariates. In two-pollutant models, associations with T2DM persisted and were only slightly attenuated for both $PM_{2.5}$ and NO_2. At exposure levels below the annual EPA NAAQS (9 $\mu g/m^3$ for $PM_{2.5}$ and 53 ppb for NO_2), positive associations between T2DM and both exposures remained. We identified multiple susceptible subpopulations including individuals with higher BMI or physical activity and those residing in lower SES neighborhoods or in the Northeast region of the US.

This study contributes to the evidence of an association between air pollution and T2DM. The single-pollutant model results were generally in agreement with the existing literature.

Table 1. Age-standardized characteristics [mean ± SD or percentage (*n* person-years)] of Nurses' Health Study ($n = 97{,}029$) and Nurses' Health Study II (111,704) cohorts of nationwide US women during follow-up from 1992 to 2019, overall and by first and fifth quintiles of $PM_{2.5}$ and NO_2 exposure.

	NHS					NHS II				
		$PM_{2.5}$		NO_2			$PM_{2.5}$		NO_2	
	Overall[a]	Q1[a]	Q5[a]	Q1[a]	Q5[a]	Overall[a]	Q1[a]	Q5[a]	Q1[a]	Q5[a]
Cases	9,702	1,470	2,039	1,772	2,018	9,381	1,958	1,428	2,131	1,587
Person-years	1,923,158	406,143	376,885	393,724	377,738	2,450,240	500,868	494,137	499,042	494,797
Age (y)[b]	67.6 ± 9.4	73.6 ± 8.3	62.4 ± 8.1	70.3 ± 9.2	64.8 ± 8.7	49.6 ± 8.7	56.6 ± 7.6	43.0 ± 6.2	53.6 ± 8.6	45.3 ± 7.4
$PM_{2.5}$ ($\mu g/m^3$)	12.1 ± 3.4	7.6 ± 1.2	17.0 ± 1.8	10.2 ± 3.2	14.5 ± 3.2	11.8 ± 3.4	7.4 ± 1.1	16.5 ± 1.7	9.4 ± 2.7	14.0 ± 3.3
NO_2 (ppb)	10.6 ± 6.6	6.5 ± 3.4	15.3 ± 9.0	4.0 ± 0.9	20.9 ± 6.3	10.5 ± 6.5	6.3 ± 3.3	16.0 ± 7.9	4.3 ± 0.9	20.3 ± 6.4
Race										
White	94 (1,760,386)	96 (357,344)	92 (344,518)	96 (359,754)	89 (334,292)	93 (2,285,834)	95 (463,398)	90 (442,498)	96 (468,836)	86 (422,190)
Non-white	6 (110,164)	4 (16,766)	8 (29,592)	4 (14,356)	11 (39,818)	7 (163,854)	5 (26,540)	10 (47,438)	4 (21,102)	14 (67,748)
Ethnicity										
Hispanic	1 (17,170)	1 (4,372)	1 (3,262)	1 (2,232)	2 (5,784)	2 (429,60)	2 (10,494)	2 (9,960)	1 (4,922)	3 (16,740)
Non-Hispanic	99 (1,853,380)	99 (369,738)	99 (370,848)	99 (371,878)	98 (368,326)	98 (2,406,728)	98 (479,444)	98 (479,976)	99 (485,016)	97 (473,198)
Postmenopausal hormone use										
Premenopausal/ never used	30 (563,294)	32 (121,036)	28 (104,404)	31 (116,860)	30 (111,074)	75 (1,846,130)	76 (370,562)	72 (350,808)	74 (363,264)	77 (376,726)
Past user	31 (580,340)	33 (122,764)	26 (96,088)	33 (124,850)	26 (97,578)	11 (275,558)	11 (53,082)	13 (62,566)	12 (57,096)	10 (50,324)
Current user	26 (480,922)	24 (89,428)	31 (115,642)	25 (92,766)	27 (100,392)	11 (262,422)	11 (53,416)	13 (65,498)	12 (56,418)	10 (47,652)
Missing	13 (245,994)	11 (40,884)	15 (57,976)	11 (39,634)	17 (65,064)	3 (65,578)	3 (12,878)	2 (11,064)	3 (13,160)	3 (15,238)
Partner's education										
More than high school	37 (699,904)	40 (151,124)	34 (127,160)	37 (137,512)	36 (132,872)	66 (1,627,226)	68 (334,404)	64 (311,840)	64 (313,226)	64 (312,140)
Less than high school	30 (549,372)	28 (103,656)	32 (118,490)	34 (126,590)	27 (101,030)	15 (354,104)	16 (77,616)	13 (63,640)	20 (100,418)	10 (52,372)
Missing	33 (621,274)	32 (119,330)	34 (128,460)	29 (110,008)	37 (140,208)	19 (468,358)	16 (77,918)	23 (114,456)	16 (76,294)	26 (125,426)
Marital status										
Married	58 (1,092,752)	61 (226,382)	57 (214,272)	64 (240,468)	53 (197,018)	53 (1,301,738)	60 (293,942)	45 (219,532)	60 (293,768)	43 (211,462)
Never married or divorced or widowed	42 (777,798)	39 (147,728)	43 (159,838)	36 (133,642)	47 (177,092)	47 (1,147,950)	40 (195,996)	55 (270,404)	40 (196,170)	57 (278,476)
Father's occupation										
Professional/ manager	26 (489,768)	29 (107,804)	24 (88,520)	25 (94,140)	26 (96,306)	22 (548,320)	25 (121,360)	19 (95,394)	20 (95,782)	23 (113,342)
Not professional or manager	74 (1,380,782)	71 (266,306)	76 (285,590)	75 (279,970)	74 (277,804)	78 (1,901,368)	75 (368,578)	81 (394,542)	80 (394,156)	77 (376,596)
BMI at baseline										
<25.0 kg/m^2	44 (820,936)	47 (174,438)	41 (155,226)	44 (165,434)	41 (154,798)	56 (1,378,538)	60 (292,750)	53 (259,230)	56 (274,994)	54 (262,570)
25.0–29.9 kg/m^2	28 (517,244)	26 (98,596)	28 (104,096)	29 (107,276)	26 (98,012)	21 (506,282)	20 (96,730)	21 (102,926)	21 (103,750)	20 (99,996)
≥30 kg/m^2	14 (256,356)	13 (49,742)	15 (54,866)	15 (54,952)	14 (51,840)	13 (327,482)	12 (56,516)	15 (74,868)	14 (68,198)	14 (67,022)
Missing	15 (276,014)	14 (51,334)	16 (59,922)	12 (46,448)	19 (69,462)	10 (237,386)	9 (43,942)	11 (52,914)	9 (42,996)	12 (60,348)
Family history of diabetes										
Yes	24 (449,670)	23 (86,444)	25 (93,206)	25 (93,636)	23 (85,702)	32 (790,066)	31 (151,220)	34 (164,584)	33 (159,320)	33 (159,740)
No	(1,420,880)	(287,666)	(280,904)	(280,474)	(288,408)	(1,659,622)	(338,718)	(325,352)	(330,618)	(330,198)
Pack-years of smoking[c]	23 ± 21	21 ± 20	26 ± 22	22 ± 20	25 ± 22	14 ± 12	13 ± 11	15 ± 13	14 ± 12	14 ± 12
Smoking status										
Never	45 (836,060)	45 (166,802)	46 (173,560)	49 (181,872)	43 (160,870)	65 (1,593,918)	67 (325,916)	64 (315,896)	67 (327,652)	62 (302,464)
Past	43 (812,350)	46 (171,514)	39 (146,362)	42 (155,286)	43 (160,440)	26 (643,232)	26 (129,064)	25 (122,714)	25 (120,638)	29 (140,868)
Current	9 (164,134)	7 (26,150)	11 (40,680)	8 (28,890)	10 (36,328)	8 (194,572)	6 (31,712)	10 (47,298)	8 (38,478)	9 (41,932)
Missing	3 (58,006)	3 (9,644)	4 (13,506)	2 (8,062)	4 (16,472)	1 (17,966)	1 (3,246)	1 (4,030)	1 (3,170)	1 (4,672)

Table 1. (*Continued.*)

	NHS					NHS II				
		$PM_{2.5}$		NO_2			$PM_{2.5}$		NO_2	
	Overall[a]	Q1[a]	Q5[a]	Q1[a]	Q5[a]	Overall[a]	Q1[a]	Q5[a]	Q1[a]	Q5[a]
Alcohol consumption (g/d)										
0	31 (578,824)	30 (110,608)	34 (125,806)	35 (131,806)	28 (105,096)	27 (670,362)	25 (123,384)	31 (150,754)	30 (147,654)	26 (124,990)
0.1–14.9	36 (673,000)	37 (139,778)	33 (124,786)	35 (129,668)	35 (131,228)	40 (972,596)	40 (196,898)	37 (182,560)	37 (179,594)	40 (195,064)
15.0–29.9	6 (111,992)	8 (30,144)	4 (14,132)	6 (23,496)	5 (18,954)	5 (121,514)	6 (31,326)	3 (16,336)	5 (24,514)	5 (22,802)
≥30.0	3 (64,066)	5 (17,840)	2 (8,950)	4 (13,776)	3 (11,308)	2 (53,558)	3 (14,386)	2 (8,756)	2 (11,522)	2 (10,140)
Missing	24 (442,668)	20 (75,740)	27 (100,438)	20 (75,364)	29 (107,524)	26 (631,658)	25 (123,944)	27 (131,530)	26 (126,656)	28 (136,942)
AHEI diet score	48.6 ± 8.6	49.6 ± 8.8	48.0 ± 8.6	48.1 ± 8.6	49.2 ± 8.7	46.6 ± 9.6	48.1 ± 9.7	46.0 ± 9.6	45.8 ± 9.6	48.0 ± 10.0
Missing	12 (223,328)	9 (33,624)	15 (56,504)	9 (32,868)	17 (62,330)	8 (206,014)	7 (32,848)	11 (51,660)	8 (37,606)	11 (52,716)
Physical activity (MET-h/wk)										
<3	15 (285,736)	14 (53,574)	15 (56,096)	15 (55,728)	16 (58,456)	13 (313,066)	12 (58,126)	15 (71,848)	13 (64,674)	13 (65,356)
3–9	16 (308,022)	17 (61,736)	16 (58,128)	17 (62,032)	16 (59,886)	16 (393,228)	15 (74,962)	16 (78,262)	16 (78,852)	16 (78,298)
9–18	15 (289,704)	16 (61,390)	14 (51,192)	16 (61,430)	14 (52,036)	16 (384,930)	16 (79,800)	15 (73,904)	16 (76,592)	15 (73,088)
18–27	10 (187,266)	12 (43,330)	8 (30,798)	11 (39,776)	9 (32,072)	10 (255,312)	11 (55,562)	9 (45,966)	10 (51,014)	10 (47,182)
27–42	9 (170,512)	11 (41,488)	7 (25,754)	10 (38,430)	8 (28,320)	10 (249,424)	12 (58,892)	8 (40,270)	10 (50,172)	9 (45,018)
≥42	9 (174,666)	13 (47,450)	6 (22,542)	11 (42,006)	7 (26,508)	12 (298,420)	16 (77,736)	9 (44,470)	13 (62,876)	11 (51,974)
Missing	24 (454,644)	17 (65,140)	35 (129,598)	20 (74,706)	31 (116,830)	23 (555,308)	17 (84,860)	28 (135,214)	22 (105,758)	26 (129,024)
Population density (per km^2)	1,148 ± 2,589	641 ± 1,375	1,848 ± 4,050	306 ± 537	2,822 ± 5,342	1,232 ± 3,426	593 ± 1,577	2,053 ± 5,128	206 ± 542	4,105 ± 8,256
Neighborhood SES score	0.0 ± 3.7	−0.8 ± 4.0	0.1 ± 3.4	−2.1 ± 3.2	1.6 ± 3.6	0.0 ± 3.7	−1.0 ± 4.1	0.1 ± 3.5	−2.5 ± 3.2	1.9 ± 3.8
Region of residence										
Northeast	45 (840,330)	36 (136,220)	40 (148,338)	40 (149,058)	51 (189,276)	30 (731,384)	28 (137,948)	23 (114,036)	22 (109,218)	41 (199,282)
Midwest	16 (290,680)	9 (35,350)	25 (94,848)	21 (79,380)	5 (17,222)	30 (725,830)	20 (99,818)	30 (144,752)	34 (168,440)	12 (57,618)
South	17 (311,226)	21 (77,934)	8 (30,374)	24 (88,264)	4 (15,924)	18 (431,752)	17 (84,436)	12 (58,342)	27 (132,412)	5 (26,124)
West	12 (228,172)	23 (85,958)	16 (58,854)	6 (23,456)	27 (101,450)	14 (348,128)	26 (126,766)	27 (130,826)	8 (39,412)	32 (156,874)
Ever moved >5 km										
Yes	33 (610,976)	51 (191,618)	17 (65,120)	46 (172,312)	17 (64,214)	48 (1,166,044)	65 (317,926)	34 (167,892)	58 (285,282)	36 (174,708)
No	67 (1,259,574)	49 (182,492)	83 (308,990)	54 (201,798)	83 (309,896)	52 (1,283,644)	35 (172,012)	66 (322,044)	42 (204,656)	64 (315,230)

Note: AHEI, Alternate Healthy Eating Index; BMI, body mass index; HR, hazard ratio; MET-h/wk, metabolic equivalent hours per week; NHS, Nurses' Health Study; NHS II, Nurses' Health Study II; NO_2, nitrogen dioxide; PM, particulate matter; $PM_{2.5}$, fine particulate matter <2.5 μm in aerodynamic diameter; SD, standard deviation.

[a]Values are means ± standard deviations for continuous variables; percentages are for categorical variables and are standardized to the age distribution of the study population. For NHS, $PM_{2.5}$ Q1 ranges from 1.1 to 9.1 $\mu g/m^3$, and Q5 ranges from 15.0 to 32.3 $\mu g/m^3$. NO_2 Q1 ranges from 0.8 to 5.4 ppb, and Q5 ranges from 14.9 to 93.0 ppb. For NHSII, $PM_{2.5}$ Q1 ranges from 1.3 to 8.8 $\mu g/m^3$, and Q5 ranges from 14.8 to 29.6 $\mu g/m^3$. NO_2 Q1 ranges from 0.7 to 5.5 ppb, and Q5 ranges from 14.3 to 87.0 ppb.

[b]Value is not age adjusted.

[c]Pack-years of smoking are reported among only smokers.

Table 2. Hazard ratios (and 95% CIs) for type 2 diabetes incidence associated with an IQR increase in $PM_{2.5}$ and NO_2 exposure averaged over the 2 years prior to diagnosis for 97,029 participants in the Nurses' Health Study, 111,704 participants in the Nurses' Health Study II, and a meta-analysis of both cohorts during follow-up from 1992 through 2019, in the full dataset and at regulatory-threshold levels of exposure.

		Single-pollutant models		Two-pollutant models	
Exposure and cohort	Cases	Basic adjusted HR (95% CI)[a]	Fully adjusted HR (95% CI)[a,b]	Basic adjusted HR (95% CI)[a]	Fully adjusted HR (95% CI)[a,b]
All exposures					
$PM_{2.5}$ (IQR = 4.9 $\mu g/m^3$)					
NHS	9,702	1.10 (1.06, 1.14)	1.04 (1.00, 1.08)	1.09 (1.05, 1.14)	1.03 (0.99, 1.08)
NHSII	9,381	1.12 (1.07, 1.17)	1.06 (1.02, 1.11)	1.09 (1.04, 1.15)	1.03 (0.98, 1.08)
NHS and NHSII[c]	19,083	1.11 (1.08, 1.14)	1.05 (1.02, 1.08)	1.09 (1.06, 1.13)	1.03 (1.00, 1.06)
P for heterogeneity		0.51	0.51	0.95	0.82
NO_2 (IQR = 7.3 ppb)					
NHS	9,702	1.03 (1.01, 1.06)	1.03 (1.00, 1.06)	1.01 (0.98, 1.03)	1.02 (0.98, 1.05)
NHSII	9,381	1.07 (1.04, 1.10)	1.07 (1.03, 1.10)	1.03 (1.00, 1.07)	1.05 (1.01, 1.10)
NHS and NHSII[c]	19,083	1.05 (1.02, 1.08)	1.05 (1.01, 1.09)	1.02 (0.99, 1.04)	1.03 (1.00, 1.07)
P for heterogeneity		0.10	0.09	0.24	0.15
Exposures below the US EPA NAAQS					
$PM_{2.5}$[d] (IQR = 1.6 $\mu g/m^3$)					
NHS	1,424	0.99 (0.92, 1.07)	0.99 (0.91, 1.08)	0.98 (0.90, 1.07)	0.98 (0.90, 1.07)
NHSII	2,166	1.07 (1.01, 1.14)	1.10 (1.03, 1.18)	1.03 (0.96, 1.11)	1.07 (1.00, 1.15)
NHS and NHSII[c]	3,590	1.03 (0.96, 1.12)	1.05 (0.95, 1.16)	1.01 (0.96, 1.07)	1.03 (0.95, 1.13)
P for heterogeneity		0.13	0.05	0.37	0.12
NO_2[e] (IQR = 7.3 ppb)					
NHS	9,697	1.03 (1.01, 1.06)	1.03 (1.00, 1.06)	1.00 (0.98, 1.03)	1.02 (0.98, 1.05)
NHSII	9,378	1.07 (1.04, 1.10)	1.07 (1.03, 1.10)	1.03 (1.00, 1.07)	1.06 (1.01, 1.10)
NHS and NHSII[c]	19,075	1.05 (1.02, 1.08)	1.05 (1.01, 1.09)	1.02 (0.99, 1.04)	1.03 (1.00, 1.07)
P for heterogeneity		0.10	0.09	0.23	0.15

Note: BMI, body mass index; CI, confidence interval; HR, hazard ratio; IQR, interquartile range; NAAQS, National Ambient Air Quality Standards; NHS, Nurses' Health Study; NHS II, Nurses' Health Study II; NO_2, nitrogen dioxide; PM, particulate matter; $PM_{2.5}$, fine particulate matter <2.5 μm in aerodynamic diameter; PMH, postmenopausal hormone; SES, socioeconomic status; T2DM, type 2 diabetes mellitus; US EPA, United States Environmental Protection Agency.
[a]Models were stratified by age and calendar year and adjusted for region of residence.
[b]Adjusted for race, family history of T2DM, individual SES (marital status, spouse's education level, father's occupation status), neighborhood SES summed *z*-score, population density, smoking status, pack-years, BMI, physical activity, diet, alcohol use, and PMH use.
[c]NHS and NHSII HRs calculated via meta-analysis using Cochran's *Q* to examine heterogeneity.
[d]Models were restricted to $PM_{2.5}$ levels below the 2024 EPA annual NAAQS of 9 $\mu g/m^3$. Table S2 provides additional information about this restricted dataset.
[e]Models were restricted to NO_2 levels below the EPA annual NAAQS of 53 ppb. Table S2 provides additional information about this restricted dataset.

Two recent meta-analyses of prospective studies each found summary HRs of 1.10 per 10 $\mu g/m^3$ of $PM_{2.5}$ exposure.[22,23] After scaling our single-pollutant $PM_{2.5}$ HRs for NHS and NHSII to 10 $\mu g/m^3$, our findings were similar in magnitude to these results [NHS HR: 1.09 (95% CI: 1.01, 1.18); NHSII HR: 1.13 (95% CI: 1.04, 1.23)]. The HR in the current study was relatively consistent with our previous analysis in NHS[21]—HR (scaled to 10 $\mu g/m^3$): 1.05 (95% CI: 0.85, 1.24)—though the present analysis achieved improved precision through additional years of follow-up, expanded geographic scope, and adjustment for neighborhood and individual SES. We also examined a 2-year rather than 1-year window of exposure. Existing studies have used various time windows to capture long-term exposure to PM air pollution. Common metrics are average annual exposures for 1 or 2 years prior to T2DM incidence or cumulative exposure during follow-up; however, there is no specific time window that has consistently produced stronger associations.[18] Results from our models using cumulative average exposure since baseline or baseline year exposure only were similar to our models using 2-year average exposure. This is in line with other studies that observed high correlations among exposure estimates across different time windows and concluded that 1- or 2-year average exposures likely serve as a good proxy for long-term exposure.[44]

Our single-pollutant model results for NO_2 and T2DM were also comparable to earlier meta-analyses with summary HRs of 1.01–1.02 per 10 $\mu g/m^3$.[22,23] Our results for NO_2, converted from parts per billion and scaled to 10 $\mu g/m^3$, were HR: 1.02 (95% CI: 1.00, 1.04) for NHS and HR: 1.05 (95% CI: 1.02, 1.07) for NHSII. The associations with $PM_{2.5}$ and NO_2 were robust, but both attenuated slightly after mutual adjustment, possibly reflecting the shared sources of these pollutants such as traffic-related emissions. A few previous studies have suggested that air pollution from traffic sources may be more important for T2DM risk than nontraffic air pollution.[14,25,45] The 2011 NHS analysis found increases in T2DM risk associated with residing <50 meters from the nearest road, a proxy for traffic-related pollutant exposures.[21] Meanwhile, in the same study, the positive associations between $PM_{2.5}$ exposure and T2DM incidence were less precise. As for studies with joint adjustment for $PM_{2.5}$ and NO_2, two analyses found that the NO_2–T2DM relationship was more robust.[34,46] More work is needed to disentangle effects of traffic vs. nontraffic pollution, which can be difficult because of the shared sources of air pollutants.[18,47]

Mechanistic research has established endothelial dysfunction, insulin resistance (IR), inflammation, and endoplasmic reticulum stress as potential pathways for the link between $PM_{2.5}$ exposure and T2DM incidence.[18] In one study, mice exposed to $PM_{2.5}$ for 24 wk exhibited markers of systemic inflammation, increased visceral adiposity, increased IR, and impaired vascular endothelial function.[48] Another study found that mice exposed to $PM_{2.5}$ for 10 wk demonstrated IR and elevated postprandial and fasting glucose levels, similar to those of mice fed a high-fat diet but exposed to clean air.[49] Other studies in mice have found IR and decreased phosphorylation of Akt in the P13K-Akt pathway, a signaling pathway for metabolism, at insulin responsive tissues.[50,51] Haberzettl et al.[52] showed that systemic IR developed in mice exposed to $PM_{2.5}$ may be mediated by pulmonary oxidative stress causing vascular IR and inflammation. Epidemiologic studies, including ones leveraging biomarker measurements, have begun to corroborate the mechanistic findings of animal models.[22] Meanwhile, the toxicological evidence elucidating the relationship between NO_2 and T2DM is more limited than that for PM, due to reactivity, correlations with other pollutants, and spatial variability.[18] The *Review of*

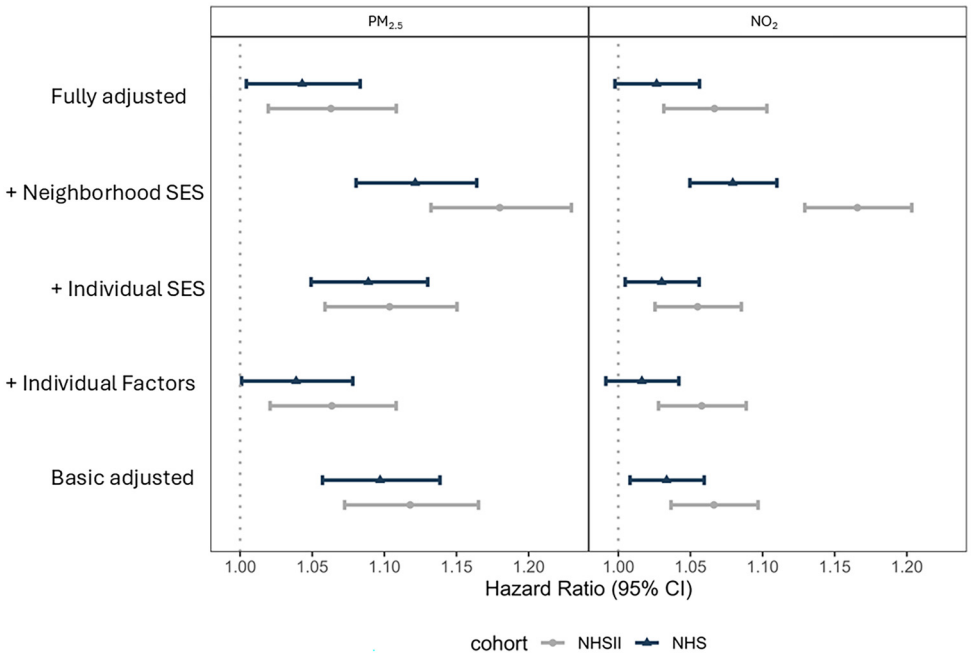

Figure 1. Hazard ratios (and 95% CIs) for type 2 diabetes incidence associated with an IQR increase in $PM_{2.5}$ and NO_2 exposure averaged over the 2 years prior to diagnosis for participants in the Nurses' Health Study (NHS) ($n = 97{,}029$) and Nurses' Health Study II (NHSII) ($n = 111{,}704$) during follow-up from 1992 to 2019, in basic adjusted models, basic adjusted models plus individual covariates or groups of covariates, and fully adjusted models. Corresponding numeric results shown in Table S7. $PM_{2.5}$ IQR = 4.9 $\mu g/m^3$; NO_2 IQR = 7.3 ppb. All models were stratified by age and calendar year and adjusted for region of residence. Fully adjusted models included race, family history of T2DM, individual SES (marital status, spouse's education level, father's occupation status), neighborhood SES summed *z*-score, smoking status, pack-years, BMI, physical activity, diet, alcohol use, and PMH use. Individual factors included race, family history of T2DM, smoking status, pack-years, BMI, physical activity, diet, alcohol use, and PMH use. Note: BMI, body mass index; CI, confidence interval; IQR, interquartile range; NHS, Nurses' Health Study; NHS II, Nurses' Health Study II; NO_2, nitrogen dioxide; PM, particulate matter; $PM_{2.5}$, fine particulate matter <2.5 μm in aerodynamic diameter; PMH, postmenopausal hormone; SES, socioeconomic status; T2DM, type 2 diabetes mellitus.

Evidence on Health Aspects of Air Pollution (REVIHAAP) Project: Technical Report points to the role of NO_2 in inflammation, airway hyper-responsiveness, and oxidative stress.[53] Other studies have linked air pollution to proinflammatory cytokines, which contribute to oxidative stress and inhibited insulin signaling.[54] Existing research in a subset of the NHS cohort found associations between NO_2 and C-reactive protein (CRP), while $PM_{2.5}$ and NO_2 were not consistently associated with hemoglobin A1c (HbA1c) in a subset of the NHS, NHSII, and HPFS.[55,56] More work is needed to elucidate biological pathways between air pollution exposure and T2DM incidence.

Ambient air pollution has experienced a long-term decline in the US in recent decades, in no small part due to implementation of, and regular updates to, the EPA NAAQS.[57] The latest EPA NAAQS released in February 2024 further strengthened the annual $PM_{2.5}$ standard from 12 $\mu g/m^3$ to 9 $\mu g/m^3$.[41] The distribution of exposures experienced in our study, with the 75th percentile at around 14.5 $\mu g/m^3$ for $PM_{2.5}$ and 13.5 ppb for NO_2, respectively, gave us ample power to examine low-level effects. When we restricted the analysis to levels below the EPA standards, the associations in both cohorts persisted. These findings are in line with other recent publications on the effects of lower level air pollutant exposures, including diabetes[46] and other chronic health outcomes.[47,58–60] In both cohorts, the associations between $PM_{2.5}$, NO_2, and incident T2DM appeared linear at levels below the EPA standard, with no evidence of a threshold. Our results contribute to the evidence of potential adverse chronic health effects at levels below the current $PM_{2.5}$ and NO_2 NAAQS. Further, the 2021 update to the World Health Organization's (WHO) Global Air Quality Guidelines (ACG) recommends annual limits of 5 $\mu g/m^3$ $PM_{2.5}$ and 10 $\mu g/m^3$ for NO_2—both below the EPA NAAQS. The 2021 WHO AQG draws on the body of evidence documenting low-level effects without thresholds, and the health benefits of reducing exposures even in areas with relatively low concentrations.[61] We unfortunately did not have sufficient statistical power to examine effects below the 2021 WHO AQG.

On both the multiplicative and additive scales, we observed EMM by time-varying BMI, with stronger associations between $PM_{2.5}$ and T2DM among individuals with BMI $\geq 30\ kg/m^2$. Similarly, we found positive RERI in the association between NO_2 and T2DM among higher BMI individuals. These results are consistent with previous studies evaluating EMM by BMI on the multiplicative scale that have found individuals with higher BMI to be more susceptible to inflammatory and impaired insulin resistance effects of air pollution.[13,62–65] Relative to individuals with a BMI $<30\ kg/m^2$, more mechanisms for the relationship between air pollution and T2DM have been elucidated among metabolically susceptible individuals, including interference with beta cell function and subcutaneous fat accumulation.[66] Our study contributes to the evidence suggesting that individuals with systemic inflammation related to higher BMI may be more susceptible to the inflammatory effects of PM air pollution. While our use of BMI is consistent with other studies of PM and T2DM, it is worth noting that BMI is an indirect measure of body fat and that other aspects may also be at play in the relationship between PM and T2DM risk, such as body fat distribution, which could be the subject of future work.

In our study, more physically active individuals experienced stronger associations between $PM_{2.5}$ and T2DM, whether EMM was assessed on the multiplicative or additive scale. Physical activity has not been as well-studied as a potential modifier of the air pollution-T2DM relationship. One previous study concluded that associations between NO_2 and T2DM were stronger among

Table 3. Hazard ratios (and 95% CIs) for type 2 diabetes incidence associated with an IQR increase in $PM_{2.5}$ or NO_2 exposure averaged over the 2 years prior to the period of diagnosis for participants in the Nurses' Health Study (NHS) and Nurses' Health Study II (NHSII) during follow-up from 1992 to 2019, stratified by BMI, smoking status, physical activity, neighborhood SES, and region.

	NHS			NHSII		
Stratification variable	Cases	$PM_{2.5}$ [HR (95% CI)][a]	NO_2 [HR (95% CI)][a]	Cases	$PM_{2.5}$ [HR (95% CI)][a]	NO_2 [HR (95% CI)][a]
BMI (kg/m^2)						
<30	4,427	0.99 (0.94, 1.04)	1.03 (0.99, 1.07)	2,360	0.90 (0.84, 0.96)	1.06 (1.01, 1.12)
≥30	4,916	1.11 (1.05, 1.16)	1.04 (1.01, 1.08)	6,594	1.11 (1.06, 1.17)	1.09 (1.05, 1.14)
Interaction term *p*-value[b]		<0.01	0.42	—	<0.01	0.35
Smoking status						
Never	4,270	1.04 (0.99, 1.09)	1.04 (1.00, 1.08)	5,832	1.04 (0.99, 1.09)	1.06 (1.02, 1.11)
Former/current	5,356	1.05 (1.00, 1.10)	1.02 (0.99, 1.06)	3,528	1.10 (1.04, 1.16)	1.07 (1.02, 1.12)
Interaction term *p*-value[b]		0.73	0.40	—	0.11	0.79
Physical activity[c]						
Q1 & Q2	6,023	1.00 (0.95, 1.04)	1.01 (0.98, 1.05)	5,830	1.04 (0.99, 1.09)	1.06 (1.02, 1.10)
Q3 & Q4	3,679	1.13 (1.07, 1.19)	1.05 (1.01, 1.09)	3,551	1.11 (1.05, 1.18)	1.08 (1.04, 1.13)
Interaction term *p*-value[b]		<0.01	0.16	—	0.03	0.45
Neighborhood SES[c]						
Q1 & Q2	5,509	1.04 (0.99, 1.08)	1.02 (0.98, 1.06)	5,827	1.08 (1.03, 1.13)	1.07 (1.03, 1.11)
Q3 & Q4	4,193	1.04 (0.99, 1.10)	1.02 (0.98, 1.06)	3,554	1.01 (0.95, 1.07)	1.04 (1.00, 1.09)
Interaction term *p*-value[b]		0.88	0.87	—	0.06	0.38
Region						
Northeast	4,551	1.11 (1.05, 1.18)	1.04 (0.99, 1.08)	2,556	1.09 (1.01, 1.17)	1.12 (1.06, 1.18)
Midwest	1,730	1.02 (0.94, 1.11)	1.09 (1.00, 1.19)	2,907	1.09 (1.02, 1.17)	1.08 (1.00, 1.16)
South	1,736	0.95 (0.87, 1.04)	1.00 (0.91, 1.09)	2,006	1.01 (0.93, 1.10)	1.11 (1.01, 1.21)
West	1,122	1.04 (0.97, 1.10)	1.04 (0.99, 1.09)	1,098	1.08 (1.01, 1.15)	1.07 (1.02, 1.13)
Interaction term *p*-value[b]		0.02	0.53	—	0.46	0.67

Note: $PM_{2.5}$ IQR = 4.9 $\mu g/m^3$; NO_2 IQR = 7.3 ppb; BMI, body mass index; CI, confidence interval; HR, hazard ratio; IQR, interquartile range; MET-h/wk, metabolic equivalent hours per week; NHS, Nurses' Health Study; NHSII, Nurses' Health Study II; NO_2, nitrogen dioxide; PM, particulate matter; $PM_{2.5}$, fine particulate matter <2.5 μm in aerodynamic diameter; PMH, postmenopausal hormone; SES, socioeconomic status; T2DM, type 2 diabetes mellitus.
[a]Adjusted for age, race, region of residence, family history of T2DM, individual SES (marital status, spouse's education level, father's occupation status), neighborhood SES summed *z*-score, smoking status, pack-years, BMI, physical activity, diet, alcohol use, and PMH use.
[b]*p*-Values presented are from multiplicative interaction terms between the covariate and $PM_{2.5}$ or NO_2 added to the fully adjusted main model.
[c]Physical activity is measured in MET-h/wk, and neighborhood SES is a composite score consisting of nine *z*-standardized variables.

physically active people, while another found no evidence for an interaction between $PM_{2.5}$ and physical activity.[11,35] As for mechanisms, some studies have suggested that more active individuals may have greater and/or better measured exposure due to increased time spent outdoors or that they are a healthier group with lower baseline hazards. At a physiological level, it is hypothesized that physical activity leads to deeper respiration, which in turn results in a larger inhaled dose of pollution.[67] A recent analysis in the NHS cohort found no evidence of an interaction between $PM_{2.5}$ exposure and physical activity in association with cardiovascular disease incidence or overall mortality.[68] Although participants reported average duration

Table 4. Relative excess risk due to interaction (RERI) for type 2 diabetes incidence associated with an IQR increase in $PM_{2.5}$ or NO_2 exposure averaged over the 2 years prior to the period of diagnosis for participants in the Nurses' Health Study (NHS) and Nurses' Health Study II (NHSII) during follow-up from 1992 to 2019, stratified by BMI, smoking status, physical activity, neighborhood SES, and region.

	NHS		NHSII	
Stratification variable	$PM_{2.5}$ [RERI (95% CI)][a]	NO_2 [RERI (95% CI)] [a]	$PM_{2.5}$ [RERI (95% CI)][a]	NO_2 [RERI (95% CI)][a]
BMI (kg/m^2)	0.33 (0.21, 0.44)	0.14 (0.02, 0.27)	0.58 (0.41, 0.76)	0.56 (0.31, 0.81)
Interaction term *p*-value[b]	<0.01	0.03	<0.01	<0.01
Smoking status	0 (−0.05, 0.05)	−0.02 (−0.06, 0.02)	0.04 (−0.02, 0.09)	−0.01 (−0.06, 0.04)
Interaction term *p*-value[b]	0.95	0.26	0.23	0.70
Physical activity[c]	0.08 (0.04, 0.12)	0.02 (−0.02, 0.06)	0.01 (−0.04, 0.06)	−0.04 (−0.08, 0)
Interaction term *p*-value[b]	<0.01	0.35	0.72	0.05
Neighborhood SES[c]	−0.01 (−0.07, 0.05)	−0.01 (−0.06, 0.03)	−0.11 (−0.19, −0.03)	−0.05 (−0.10, 0)
Interaction term *p*-value[b]	0.76	0.58	0.01	0.06
Region				
Northeast	0.16 (0.08, 0.23)	0.05 (−0.03, 0.13)	0.04 (−0.05, 0.13)	0.09 (0.02, 0.16)
Interaction term *p*-value[b]	<0.01	0.24	0.36	0.02
Midwest	−0.05 (−0.15, 0.05)	0.07 (−0.02, 0.15)	0.03 (−0.04, 0.09)	0.04 (−0.04, 0.12)
Interaction term *p*-value[b]	0.33	0.13	0.42	0.30
South	−0.11 (−0.24, 0.02)	−0.03 (−0.13, 0.08)	−0.06 (−0.17, 0.06)	0.07 (−0.04, 0.18)
Interaction term *p*-value[b]	0.11	0.63	0.34	0.19
West	−0.02 (−0.10, 0.06)	0.01 (−0.05, 0.06)	0 (−0.07, 0.07)	−0.01 (−0.07, 0.04)
Interaction term *p*-value[b]	0.59	0.77	0.93	0.63

Note: $PM_{2.5}$ IQR = 4.9 $\mu g/m^3$; NO_2 IQR = 7.3 ppb. The reference levels for stratification variables were defined as BMI <30, never smoker, physical activity below the median, and nSES below the median. RERI for each region was assessed relative to the other regions. BMI, body mass index; CI, confidence interval; DM, diabetes mellitus; HR, hazard ratio; IQR, interquartile range; MET-h/wk, metabolic equivalent hours per week; NHS, Nurses' Health Study; NHSII, Nurses' Health Study II; NO_2, nitrogen dioxide; PM, particulate matter; $PM_{2.5}$, fine particulate matter <2.5 μm in aerodynamic diameter; PMH, postmenopausal hormone; SES, socioeconomic status; T2DM, type 2 diabetes mellitus.
[a]Adjusted for age, race, region of residence, family history of DM, individual SES (marital status, spouse's education level, father's occupation status), neighborhood SES summed *z*-score, smoking status, pack-years, BMI, physical activity, diet, alcohol use, and PMH use.
[b]*p*-Values presented are tested for the additive interaction terms.
[c]Physical activity is measured in MET-h/wk, and neighborhood SES is a composite score consisting of nine *z*-standardized variables.

and intensity of physical activity, we lack more detailed information on each activity or air pollution exposure specific to times when participants were exercising, making it more difficult to detect any potential interactions.

In terms of EMM by neighborhood-level factors, we found evidence of an additive interaction between nSES and $PM_{2.5}$ in association with T2DM in NHSII. The finding that individuals residing in lower nSES neighborhoods were at greater risk matches the conclusion from one previous study that applied an additive hazards model and evaluated interactions by individual education level, income, and financial stress.[69] Individuals with lower income or residing in lower income areas may be more susceptible to T2DM risk due to less healthy lifestyles and higher BMI, which in turn increase risk for cardiovascular comorbidities. It is also possible that lower SES individuals are diagnosed with T2DM later due to less frequent doctor visits or lowered ability to act on initial symptoms due to time and financial constraints.[69] Other studies, which assessed EMM on the multiplicative scale by individual education level, had mixed results, ranging from no evidence of an interaction to higher risk for those with higher education levels.[11,35,65] However, none of these studies focused on EMM by neighborhood-level SES.

Lastly, we observed multiplicative and additive EMM of the $PM_{2.5}$–T2DM association by region in NHS, with higher risk for participants residing in the Northeast compared to those residing in the Midwest, South, or West. These regional differences in risk may be due to variation in sources of $PM_{2.5}$ and their associated particle constituents.[70,71]

This study has several limitations. In terms of generalizability, participants in NHS and NHSII cohorts are middle-aged or older, primarily well-educated non-Hispanic white women, who were recruited as registered nurses. Though the mechanisms have not been elucidated, previous research has suggested that women may be more susceptible to the effects of air pollution exposure on diabetes risk.[23–25] Our findings may not be representative of male or more racially or socioeconomically diverse populations with different distributions of exposures, confounders, and effect modifiers. However, the well-defined study population also limits the potential for confounding by these factors. As for exposure measurement, we applied models with high predictive accuracy, spatiotemporal resolution, and wide geographic coverage. Some level of measurement error may have been introduced by the lack of available monitoring data for $PM_{2.5}$ before 1999 as well as by our reliance on residential addresses, as they do not capture all locations where an individual might be exposed. However, it is likely that any exposure measurement error attributable to the use of ambient measurements was nondifferential and likely pushed estimates toward the null.[72] Our study considered $PM_{2.5}$ and NO_2 in joint models to reduce the possibility of unmeasured confounding by co-pollutants. Several recent studies have accounted for other environmental variables, such as normalized difference vegetation index (NDVI) or greenness and noise and provide mixed results.[73–75] Disentangling the complex interrelationships between environmental co-exposures and their association with T2DM and other cardiometabolic outcomes is an active area of research and represents an important step in future studies.

This study has some important strengths. We were able to utilize two large cohorts over a 27-year follow-up period to examine the associations of air pollution with incident T2DM among women—a group that is believed to be more susceptible. Participants in the NHS and NHSII represent a wide geographic distribution across the US. We were able to examine long-term exposures over various time windows with high spatial resolution. While the distribution of PM and NO_2 exposure levels in our US-based study population is lower in magnitude than global levels, we leveraged the low-level data to evaluate whether associations persist at levels below the current EPA standards. Our results contribute evidence that even small increases in long-term air pollution levels could contribute to T2DM risk. The outcome, self-reported clinician diagnosis of diabetes, is highly reliable, with 98% of questionnaire-confirmed cases reconfirmed by medical review in NHSII in a validation study.[27] Similar medical record reviews have been completed for the NHS, demonstrating the validity of the supplemental questionnaire for T2DM diagnosis.[76] An analysis of fasting plasma glucose and fructosamine in 200 randomly selected participants who did not report having diabetes found a false negative rate of only 0.5%. The richness of the dataset enabled robust adjustment for time-varying confounders at the individual and area level, as well as examination of potential effect modifiers on the multiplicative and additive scales, further illuminating complex relationships. The influence of adjustment for nSES on the association between air pollution and T2DM demonstrates the importance of including not only individual but also area-level SES confounders wherever possible, as has been suggested in earlier reviews.[24]

Conclusions

In two cohorts of US women, we observed that an increase in long-term ambient residential $PM_{2.5}$ or NO_2 exposure was associated with a modest increased risk of T2DM. Positive associations between $PM_{2.5}$ and T2DM and NO_2 and T2DM persist at levels below the EPA NAAQS.

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Access to the Nurses' Health Study and Nurses' Health Study II requires the proposal and approval of the specific research project and is not directly sharable. Details on obtaining access are available at https://nurseshealthstudy.org/researchers.

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